

REMARKS

1. Sequence Rules

The Specification has been amended at Tables I and II on page 11 of the Specification to insert appropriate "SEQ ID NO:" identifiers.

No new matter has been added.

2. Status of the Claims

Claims 1-16 are pending. Claims 10 and 16 are herein cancelled. Claims 12-14 are herein withdrawn. Claims 1-9, 11 and 15 are herein amended.

The Examiner has objected to claim 1 because it is missing a period at the end of the claim. Accordingly, claim 1 has been amended to add a period at the end of the claim.

The Examiner has objected to claim 4 because the term "FIX" is unclear. Accordingly, claim 4 has been amended to add the term "factor IX."

3. Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claim 11 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement and written description, both with respect to "derivatives" of human factor VIII. Applicants have deleted the terms "derivatives" in claim 11.

Although not conceding the propriety of the rejections, by amending the claim, Applicants have obviated the Examiner's rejection.

The Examiner has rejected claim 16 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the Specification sufficiently to provide enablement for a host cell in a human body.

Applicants have cancelled claim 16. Accordingly, the rejection should be withdrawn.

4. Rejections Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 1-8, 11, 15-16 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to point out distinctly claimed subject matter which Applicants regard as the invention with respect to several claim terms.

4.1. Applicants have amended claims 1-8, 11, 15-16 to replace the expression “characterized in that” by the term “wherein.” Accordingly, the rejection should be withdrawn.

4.2. The Examiner has rejected claim 8 under 35 U.S.C. § 112, second paragraph, as containing insufficient antecedent basis for the limitation “the human factor VIII” in the claim and its dependent claims. Additionally, claim 8 recites amino acid residues without the term “SEQ ID NO.”

Applicants have amended claim 8 to replace the expression “it comprises a first DNA segment coding for the amino acids 1 through 740 of the human factor VIII and a second DNA segment coding for the amino acids 1649 through 2332 of the human factor VIII” by the expression “it represents a recombinant factor VIII lacking the middle heavily glycosylated region of the factor VIII polypeptide chain residing between amino acids Arg-740 and Glu-1649.” Support for this amendment can be found in paragraph [0006] of the application as published. The claim does not recite for or more amino acids, so it is believe that no SEQ ID NO. is required. Accordingly, the rejection should be withdrawn.

4.3. The Examiner has rejected claim 11 under 35 U.S.C. § 112, second paragraph, as it recites a biologically active recombinant human factor and is dependent on claim 10, which does not recite a modified human factor VIII cDNA. Applicants have amended claim 11 to incorporate the features of claim 10 to recite the expression “that comprises the following steps...” Claim 10 is cancelled. Accordingly, the rejection should be withdrawn.

Claim 15 has been amended to depend on claim 11.

Furthermore, Applicants have made the following amendments:

- Claim 9 is amended to remove the multiple dependencies.
- Claim 1 is amended to recite the term “A” before the expression “modified factor VIII.”
- Claims 2-8 are amended to recite the term “the” before the expression “modified factor VIII.”

- Claim 9 is amended to recite the term "A" before the expression "recombinant expression vector."
- Claim 11 is amended to recite the term "A" before the expression "process for the production."

5. Rejections under 35 U.S.C. § 102

5.1. Claims 1-6, 8-11 and 15-16 are rejected under 35 U.S.C. § 102 (a) and 102 (e) as being anticipated by Negrier *et al.* (U.S. 2003/0083257). Applicants respectfully disagree for at least the following reasons:

U.S. 2003/0083257 describes a factor VIII cDNA, the B domain of which has been deleted, and wherein a truncated factor IX intron has been inserted. More particularly, US 2003/0083257 describes 5 constructs, corresponding to a factor VIII cDNA modified such that it comprises the insertion of the FIX truncated intron 1 within one of the FVIII intron 1, 12 or 13 location, or within both the FVIII introns 1 and 12 locations, or both the FVIII introns 1 and 13 locations. U.S. 2003/0083257 nevertheless fails to disclose or to suggest the further modification of the described constructs by the insertion of an additional intron downstream the promoter and upstream of the modified FVIII cDNA.

Applicants, therefore, submit that U.S. 2003/0083257 fails to disclose the subject matter of claim 1, since a document could only be considered as anticipatory when it contains all of the claimed features. In view of this, Applicants submit that the subject matter of claims 1-6, 8-11 and 15-16 is novel with respect to the disclosure of U.S. 2003/0083257.

Withdrawal of the corresponding rejection is thus respectfully requested.

5.2. Claims 1-6 and 9-11 are rejected under 35 U.S.C. § 102 (b) as being anticipated by Plantier *et al.* (2001 Thromb Haemost). Applicants respectfully disagree for at least the following reasons:

Plantier *et al.* corresponds to the scientific publication of the results described in Negrier *et al.* (U.S. 2003/0083257) and the technical contents of these two prior art documents are highly

similar. Furthermore, Plantier *et al.* explicitly disclose that the expression of factor VIII protein directly depends from the site wherein the truncated FIX intron 1 is inserted (see Plantier *et al.*, page 602, left column, 5th paragraph), since unfavourable insertion locations could result in decreased expression of the protein. Finally, Plantier *et al.* explicitly suggest that FVIII production could be further increased by the improvement of FVIII secretion or by the reduction of FVIII binding to cellular chaperones (see Plantier *et al.*, page 602, right column, end of 2nd paragraph).

Plantier *et al.* nevertheless fails to disclose or to suggest the further modification of the described constructs by the insertion of an additional intron downstream the promoter and upstream of the modified FVIII cDNA.

Applicants, therefore, submit that Plantier *et al.* fail to disclose the subject matter of claim 1, since a document could only be considered as anticipatory when it contains all of the claimed features. In view of this, Applicants submit that the subject matter of claims 1-6 and 9-11, is novel with respect to the disclosure of Plantier *et al.*

Withdrawal of the corresponding rejection is thus respectfully requested.

5.3. Claims 1-6, 9-11 and 15 are rejected under 35 U.S.C. § 102 (b) as being anticipated by Negrier *et al.* (U.S. 6,271,025). Applicants respectfully disagree for at least the following reasons:

U.S. 6,271,025 describes a factor VIII cDNA, the B domain of which has been deleted, and wherein a truncated factor IX intron has been inserted. More particularly, U.S. 6,271,025 describes constructs, corresponding to a factor VIII cDNA modified such that it comprises the insertion of the FIX truncated intron 1 within the FVIII intron 1, 12 or 13 location. U.S. 6,271,025 nevertheless fails to disclose or to suggest the further modification of the described constructs by the insertion of an additional intron downstream the promoter and upstream of the modified FVIII cDNA.

Applicants, therefore, submit that U.S. 6,271,025 fails to disclose the subject matter of claim 1, since a document could only be considered as anticipatory when it contains all of the claimed features. In view of this, Applicants submit that the subject matter of claims 1-6, 9-11

and 15, is novel with respect to the disclosure of U.S. 6,271,025.

Withdrawal of the corresponding rejection is thus respectfully requested.

5.4. Claims 1-6, 9-11 and 15 are rejected under 35 U.S.C. § 102 (e) as being anticipated by Negrier *et al.* (U.S. 6,800,461). Applicants respectfully disagrees for at least the following reasons:

U.S. 6,800,461 teaches a process for producing a factor VIII cDNA, the B domain of which has been deleted, and wherein a truncated factor IX intron has been inserted. More particularly, U.S. 6,800,461 describes constructs, corresponding to a factor VIII cDNA modified such that it comprises the insertion of the FIX truncated intron 1 within the FVIII intron 1, 12 or 13 location. U.S. 6,800,461 nevertheless fails to disclose or to suggest the further modification of the described constructs by the insertion of an additional intron downstream the promoter and upstream of the modified FVIII cDNA.

Applicants, therefore, submit that U.S. 6,800,461 fails to disclose the subject matter of claim 1, since a document could only be considered as anticipatory when it contains all of the claimed features. In view of this, Applicants submit that the subject matter of claims 1-6, 9-11 and 15, is novel with respect to the disclosure of U.S. 6,800,461.

Withdrawal of the corresponding rejection is thus respectfully requested.

5.5. Claims 1-6, 9-11 and 15 are rejected under **35 U.S.C. § 102 (e)** as being anticipated by Negrier *et al.* (U.S. 6,780,614). Applicants respectfully disagree for at least the following reasons:

U.S. 6,780,614 describes a factor VIII cDNA, the B domain of which has been deleted, and wherein a truncated factor IX intron has been inserted. More particularly, U.S. 6,780,614 describes constructs, corresponding to a factor VIII cDNA modified such that it comprises the insertion of the FIX truncated intron 1 within the FVIII intron 1 or 13 location. U.S. 6,780,614 nevertheless fails to disclose or to suggest the further modification of the described constructs by the insertion of an additional intron downstream the promoter and upstream of the modified FVIII cDNA.

Applicants, therefore, submit that U.S. 6,780,614 fails to disclose the subject matter of claim 1, since a document could only be considered as anticipatory when it contains all of the claimed features. In view of this, Applicants submit that the subject matter of claims 1-6, 9-11 and 15, is novel with respect to the disclosure of U.S. 6,780,614.

Withdrawal of the corresponding rejection is thus respectfully requested.

6. Claims Rejection under 35 U.S.C. § 103

6.1. Claim 7 is rejected under 35 U.S.C. § 103 (a) as being unpatentable over Negrier *et al.* (U.S. 2003/0083257). Applicants respectfully disagree for at least the following reasons:

U.S. 2003/0083257 also discloses a factor VIII cDNA, the B domain of which has been deleted, and wherein the FVIII introns 1 and 13 locations were replaced either by:

- the first intron of the apolipoprotein A1 gene or;
- by the first intron of the β -globin gene.

As shown in the example (page 6, paragraph [0045]), two different constructions of FVIII are presented:

- the first construction contains apolipoprotein A1 intron in position 1 and 13 ; and
- the second construction contains β -globin intron in position 1 and 13.

U.S. 2003/0083257 nevertheless fails to disclose or to suggest the use of β -globin intron 2 and the further modification of the described constructs by the insertion of an additional intron downstream the promoter and upstream of the modified FVIII cDNA.

Therefore, even in view of U.S. 2003/0083257, the person of ordinary skill would have had neither incentive nor reasonable expectation of success to obtain a synergistic effect between the combined insertion of an intron between the promoter and the coding sequence and of two introns within said coding sequence (the 3 intron construct as shown in paragraph 50 of the published application) since U.S. 2003/0083257 is focused on the preparation of modified FVIII cDNA constructs and fails to disclose any experimental results concerning the expression of the corresponding FVIII protein.

Finally, Applicants submit that none of the teachings of U.S. 2003/0083257, Plantier *et*

al., U.S. 6,271,025, U.S. 6,800,461, or U.S. 6,780,614 taken alone or in combination, would have actually indicated or suggested to the person of ordinary skill in the art to prepare a modified factor VIII cDNA wherein introns 1 and 13 are replaced by spliceable nucleotide sequences, and wherein another spliceable nucleotide sequence is inserted downstream of the promoter sequence and upstream of the modified factor VIII cDNA. Moreover, considering the fact that none of these documents actually provide any argument or any result that might have provided the skilled person with a reasonable expectation of success to obtain a synergistic effect with such a construct, Applicants submit that the claims of the present application are non-obvious/inventive with respect to the cited prior art documents.

Consequently, claim 1 is necessarily non-obvious, as also are dependent claims 2 - 9, 11 and 15 which all (directly or indirectly) include the limitations of claim 1.

Withdrawal of the corresponding rejection is thus respectfully requested.

7. Non-Statutory Double Patenting Rejections

The Examiner has provisionally rejected claim 6 for obviousness-type double patenting over Negrier '461 and rejected claims 1-6 and 11 for obviousness type-double patenting over claims 1-4 of Negrier '614. Applicants respectfully traverse.

As discussed above in response to the rejections under 35 U.S.C. § 103 in view of the teachings of U.S. 2003/0083257, Plantier *et al.*, U.S. 6,271,025, U.S. 6,800,461, or U.S. 6,780,614 these references do not give guidance or evidence that a skill artisan would reasonably expect to succeed in further increasing the expression yield of factor VIII by further introducing a spliceable nucleotide sequence downstream of the promoter and upstream of the coding sequence for factor VIII, compared to prior art.

Thus, one skilled in the art would have no motivation to modify the teachings of the prior art to lead to the claimed 3 intron construct.

Applicants respectfully submit that claims 1-6 and 11 are patentably distinct from Negrier '461 and '614, and request that the rejection be withdrawn.

In view of the foregoing remarks, Applicants respectfully request the reconsideration of this application and timely allowance of the pending claims.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicants respectfully petition for a one (1) month extension of time for filing a reply in connection with the present application, and the required fee of \$130.00 is attached hereto.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Leonard R. Svensson Reg. No. 30,330 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

By 

Leonard R. Svensson

Registration No.: 30,330

BIRCH, STEWART, KOLASCH & BIRCH, LLP

12770 High Bluff Drive

Suite 260

San Diego, California 92130

(858) 792-8855

Attorney for Applicants